

# Lightweight noninvasive trauma monitor for early indication of central hypovolemia and tissue acidosis: A review

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<b>BACKGROUND:</b>	Hemorrhage is a major cause of soldier death; it must be quickly identified and appropriately treated. We developed a prototype patient monitor that noninvasively and continuously determines muscle oxygen saturation ( $S_{mO_2}$ ), muscle pH ( $pH_m$ ), and a regional assessment of blood volume (HbT) using near-infrared spectroscopy. Previous demonstration in a model of progressive, central hypovolemia induced by lower body negative pressure (LBNP) showed that $S_{mO_2}$ provided an early indication of impending hemodynamic instability in humans. In this review, we expand the number of subjects and provide an overview of the relationship between the muscle and sublingual microcirculation in this model of compensated shock.
<b>METHODS:</b>	Healthy human volunteers ( $n = 30$ ) underwent progressive LBNP in 5-minute intervals. Standard vital signs, along with stroke volume (SV), total peripheral resistance, functional capillary density, $S_{mO_2}$ , HbT, and $pH_m$ were measured continuously throughout the study.
<b>RESULTS AND DISCUSSION:</b>	$S_{mO_2}$ and SV significantly decreased during the first level of central hypovolemia ( $-15$ mm Hg LBNP), whereas vital signs were later indicators of impending cardiovascular collapse. $S_{mO_2}$ declined with SV and inversely with total peripheral resistance throughout LBNP. HbT was correlated with declining functional capillary density, suggesting vasoconstriction as a cause for decreased $S_{mO_2}$ and subsequently decreased $pH_m$ .
<b>CLINICAL TRANSLATION:</b>	The monitor has been miniaturized to a 58-g solid-state sensor that is currently being evaluated on patients with dengue hemorrhagic fever. Early results demonstrate significant decreases in $S_{mO_2}$ similar to those observed with progressive reductions in central blood volume. As such, this technology has the potential to (1) provide a monitoring capability for both nontraumatic and traumatic hemorrhage and (2) help combat medics triage casualties and monitor patients during lengthy transport from combat areas. ( <i>J Trauma Acute Care Surg.</i> 2012;73: S106–S111. Copyright © 2012 by Lippincott Williams & Wilkins)
<b>KEY WORDS:</b>	Lower body negative pressure; shock; medical monitoring; vasoconstriction.

Hemorrhagic shock remains a primary cause of death in both civilian and military trauma.<sup>1–3</sup> Early intervention with actions to recognize and control bleeding with adequate fluid resuscitation could prove critical in reducing morbidity and mortality. Unfortunately, early and accurate diagnosis of internal hemorrhage can be limited when using routine vital signs (e.g., pulse oximetry [ $SpO_2$ ], arterial blood pressure, heart rate [HR], mental status) that are typically late indicators of impending shock.<sup>4</sup> New medical monitoring capabilities that provide measures of changes in peripheral tissue metabolism

are needed to bridge the capability gap for an early indication of reduced central blood volume.

Arterial vasoconstriction represents a compensatory mechanism designed to maintain adequate perfusion pressure to vital organs such as the brain and heart. As this vasoconstrictor response reduces blood flow and oxygen delivery to peripheral tissues,<sup>5,6</sup> noninvasive assessment of muscle metabolic markers (e.g., oxygen, pH) could advance our diagnostic capability for earlier detection of blood volume loss and guidance of fluid resuscitation.

When blood flow to the peripheral muscles is decreased as a result of regional vasoconstriction, an increase in relative (percent) extraction of the total oxygen delivered in the blood to the tissue is reflected in an absolute reduction in muscle hemoglobin oxygen saturation ( $S_{mO_2}$ ),<sup>5</sup> which can be determined noninvasively with near-infrared spectroscopy (NIRS). Using NIRS,  $S_{mO_2}$  is calculated as a percentage of oxygenated hemoglobin in the volume of total hemoglobin (HbT), which is detected by the optical sensor.<sup>7</sup> Muscle hydrogen ion concentration ( $pH_m$ ) can also be determined simultaneously from the same NIR spectrum.<sup>8,9</sup> The measurement of tissue pH is important as a diagnostic and therapeutic tool because it is significantly more sensitive to the development of shock than measures of arterial and venous pH,<sup>6</sup> and depressed tissue pH is associated with negative outcomes.<sup>10</sup> As such, NIRS technology designed to measure  $S_{mO_2}$  and  $pH_m$  as the core of

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The LBNP study was conducted under a protocol reviewed and approved by the Brooke Army Medical Center Institutional Review Board and in accordance with the approved protocol.

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a small and portable device could prove useful for rapid, noninvasive patient assessment both inside and outside the hospital.

In this review of a series of experiments conducted in the Human Physiology Laboratory at the US Army Institute of Surgical Research, we describe the use of NIRS technology to determine the efficacy of measuring  $S_{mO_2}$  and  $pH_m$  as early indicators of reduced central blood volume in human subjects during exposure to lower body negative pressure (LBNP) as a model of preshock hemorrhage.<sup>11</sup> Previously,  $S_{mO_2}$  was found to be significantly different from baseline values at levels of simulated blood loss before changes in standard vital sign measures such as HR, blood pressure, and  $SpO_2$ .<sup>12</sup> In this model, we also demonstrated a significant reduction in  $pH_m$  when  $S_{mO_2}$  reached a critically low level.<sup>12</sup> In this review article, we supplement the results from a larger group of subjects studied under the same protocol and examine the relationship between HbT and measures of vasoconstriction initially reported in a companion study.<sup>13</sup> Our objective was to provide new insight into the underlying physiology of how compensatory reductions in total peripheral resistance (TPR) and functional capillary density (FCD) are associated with reduced HbT,  $S_{mO_2}$ , and muscle pH during simulated hemorrhage in humans.

## METHODS

### Protocol

All procedures and risks associated with these experiments were explained to the research subjects, and their voluntary written informed consent was obtained. With the use of a neoprene skirt designed to form an airtight seal between the subject and the chamber, the application of negative pressure to the lower body (below the iliac crest) results in a redistribution of blood away from the upper body (head and heart) to the lower extremities and abdomen. This model provides conditions of controlled, experimentally induced hypovolemic hypotension, offering a valuable method for investigating monitoring devices such as NIRS.

Each subject reported once to the laboratory for a progressive LBNP protocol. The subject was first instrumented with noninvasive devices to measure HR, stroke volume (SV),  $SpO_2$ , and NIRS to calculate  $S_{mO_2}$ , HbT, and  $pH_m$ . The LBNP protocol consisted of a 5-minute baseline period followed by 5 minutes of chamber decompression to  $-15$  mm Hg,  $-30$  mm Hg,  $-45$  mm Hg, and  $-60$  mm Hg and additional increments of  $-10$  mm Hg every 5 minutes until either the onset of cardiovascular collapse or the completion of 5 minutes at  $-100$  mm Hg. Cardiovascular collapse was defined by a fall in systolic blood pressure (SBP) to less than 80 mm Hg concurrent with the onset of presyncopal symptoms such as bradycardia, sweating, nausea, dizziness, tunnel vision, or gray-out (loss of color vision). At the onset of cardiovascular collapse, the chamber vacuum was released to ambient pressure to rapidly restore blood flow to the central circulation. To ensure subject safety, an Advanced Cardiac Life Support–certified clinician was present in the laboratory building during all LBNP tests.

### Hemodynamic Measurements

Continuous HR was measured from a standard electrocardiogram (ECG). Beat-by-beat SBP and diastolic blood pres-

sure were measured noninvasively using an infrared finger photoplethysmograph (Finometer Blood Pressure Monitor; TNO-TPD Biomedical Instrumentation, Amsterdam, the Netherlands). The Finometer blood pressure cuff was placed on the middle finger of the left hand, which, in turn, was laid at heart level. Arterial oxygen saturation ( $SpO_2$ ) was measured using pulse oximetry (BCI Capnograph Plus; Smiths Medical, Waukesha, WI). Beat-to-beat SV was measured noninvasively using thoracic electrical bio-impedance with an HIC-2000 Bio-Electric Impedance Cardiograph (Bio-Impedance Technology, Chapel Hill, NC). Total peripheral resistance was calculated as mean arterial pressure divided by the product of HR and SV. Data presented for each of these parameters represent the average values taken over the last 3 minutes of baseline and each LBNP level.

Functional capillary density was determined using side stream dark field video microscopy (MicroScan; MicroVision Medical, Inc, Wallingford, PA). The probe was placed on the sublingual fossa and small blood vessels ( $<25$   $\mu$ m) were imaged and recorded on a digital video recorder, and FCD was calculated.<sup>13</sup>

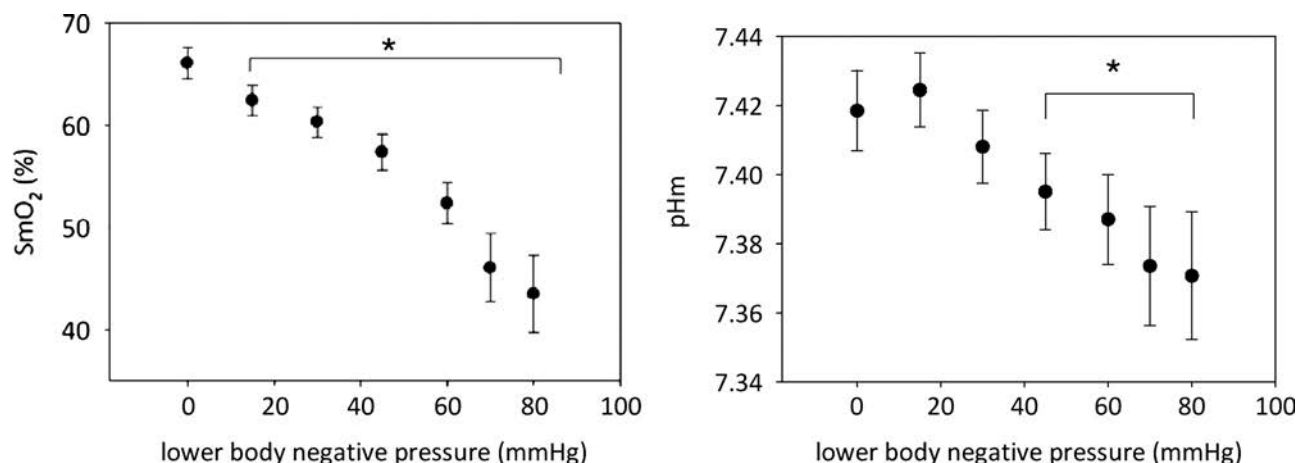
### Noninvasive Determination of $S_{mO_2}$ , HbT, and $pH_m$

$S_{mO_2}$ , HbT, and  $pH_m$  were determined noninvasively using a NIRS monitor developed jointly by personnel from the Anesthesiology Department of the University of Massachusetts Medical School (UMMS System, Worcester, MA) and Luxtec Corporation (West Boylston, MA). This spectroscopic technique was previously validated for  $S_{mO_2}$  and HbT using simulated spectra and in vitro laboratory experiments (phantoms),<sup>7</sup> and the  $pH_m$  technique was validated across multiple subjects during handgrip exercise.<sup>14</sup> The UMMS NIRS system in this study uses additional mathematical preprocessing techniques to correct spectra for variation in skin pigmentation, fat, and muscle optical properties before the calculation of  $S_{mO_2}$ , HbT, and  $pH_m$ . The optical sensor collects NIR reflectance spectra from deep within the forearm muscle (flexor digitorum profundus) every  $\sim 20$  seconds. The spectra are then processed with calibration equations contained in a dedicated computer.  $S_{mO_2}$ , HbT, and  $pH_m$  are simultaneously calculated from each spectrum, displayed as a trend, and stored on a hard drive contained in the system. A detailed description of the UMMS system has been previously published.<sup>12</sup>

A cohort of eight subjects had previously been exposed in our laboratory to the same LBNP protocol, whereas tissue  $Sto_2$  was measured using the commercially available NIRS InSpectra Tissue Spectrometer (Hutchinson Technologies, Hutchinson, MN).<sup>15</sup> The InSpectra probe was placed on intact skin over the *thenar eminence* muscle of the left hand following the manufacturer's instructions. Subsequently, we compared oxygen saturation measurements made with the UMMS system to those determined by the InSpectra probe by choosing subjects from our large UMMS cohort that matched the InSpectra subjects on the basis of sex, reduction in SV during LBNP, and age.<sup>15</sup>

## RESULTS

Complete NIRS data sets using the UMMS system were obtained from 27 of the 30 subjects that entered the study.



**Figure 1.** Near-infrared spectroscopy determined  $S_{mO_2}$  (A) and  $pH_m$  (B) during LBNP. Values are mean  $\pm$  SE for all subjects ( $n = 27$ ). Negative pressure is increased progressively from baseline (0). \*Levels different from baseline at  $p < 0.05$ .

Near-infrared spectroscopy data were not obtained for 2 subjects, and 1 subject had poor spectral quality. Functional capillary density data were obtained on 16 of these subjects, and these results were previously published.<sup>13</sup> In the entire set of subjects measured with the UMMS system ( $n = 27$ ), SV decreased in a near linear fashion with increasing LBNP (see Figure, Supplemental Digital Content 1, <http://links.lww.com/TA/A132>). Significant decreases in MAP were observed at a negative pressure of  $-60$  mm Hg, whereas significant elevations in HR were observed at  $-45$  mm Hg (see Figure, Supplemental Digital Content 1, <http://links.lww.com/TA/A132>).  $SpO_2$  did not change from baseline throughout LBNP (data not shown).

Figure 1 shows changes in the NIRS-derived parameters during progressive reductions in central blood volume.  $S_{mO_2}$  decreased continually during LBNP with a significant decrease occurring at the first level ( $-15$  mm Hg) of negative pressure. A significant decrease in  $pH_m$  was observed at  $-45$  mm Hg. Figure 2 demonstrates that, although progressive reductions in  $S_{mO_2}$  were obtained using the UMMS system, the commercially available InSpectra probe measurement of  $StO_2$  did not change throughout LBNP.

Figure 3 illustrates the relationship of  $S_{mO_2}$  measured with the UMMS system with SV (A) and with TPR (B). The amalgamated correlation coefficient between  $S_{mO_2}$  and SV (positive relationship) was  $R^2 = 0.92$  and between  $S_{mO_2}$  and TPR (negative relationship) was  $R^2 = 0.96$ .

Both HbT and FCD decreased during LBNP, producing a positive linear relationship ( $R^2 = 0.89$ ), with smaller FCD corresponding to lower HbT (Fig. 4).

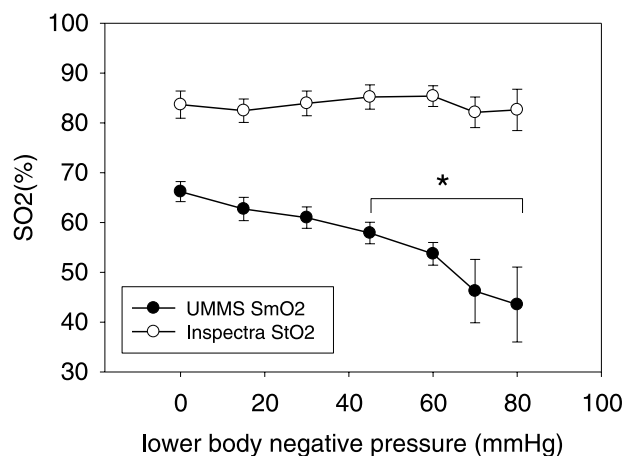
## DISCUSSION AND CONCLUSIONS

Using NIRS technology, these experiments demonstrated that muscle oxygenation decreases in proportion with reductions in central blood volume as evidenced by the strong positive relationship between the decreases in  $S_{mO_2}$  and SV throughout the course of the LBNP protocol. Perhaps of more clinical diagnostic significance was the observation that  $S_{mO_2}$  was one of the earliest indicators of progressive central hypovolemia compared with delayed alterations in standard vital

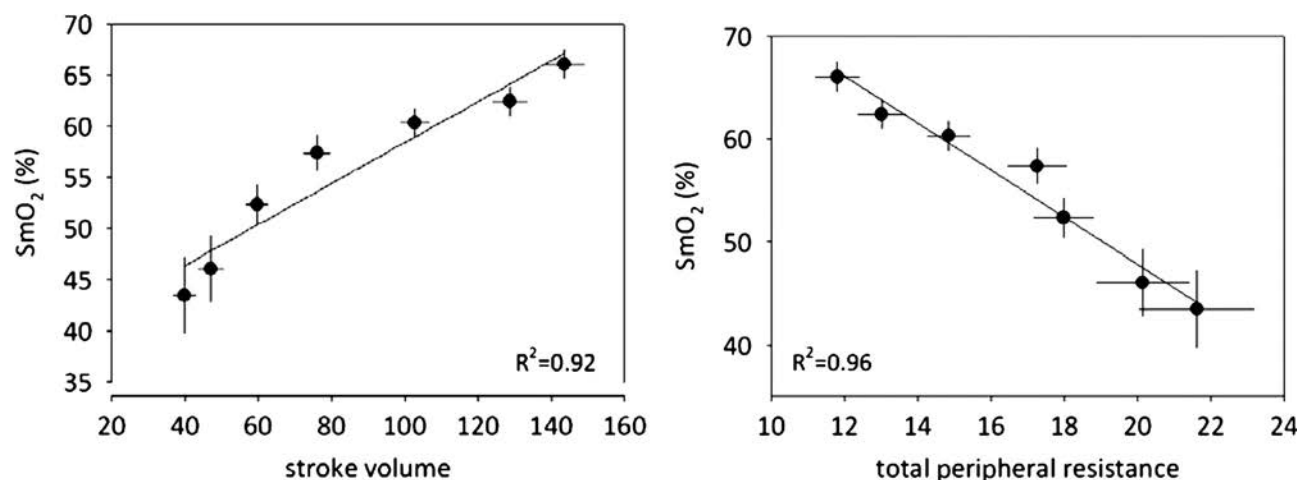
signs (e.g., HR, BP,  $SpO_2$ ). We also demonstrated a small but significant reduction in NIRS-measured  $pH_m$  when  $S_{mO_2}$  reached a critically low level. The results also provide insight into the underlying physiology of the response to simulated hemorrhage in humans: the increase in TPR characterized by a decrease in FCD, resulting in reduced peripheral blood volume, tissue oxygenation, and development of muscle acidosis.

The observed linear relationship with SV suggests that the noninvasive  $S_{mO_2}$  measurement is a sensitive marker of reduced central volume and delivery of blood to peripheral tissues during central hypovolemia. In addition, the inverse linear relationship between  $S_{mO_2}$  and TPR implies that skeletal muscle vasoconstriction and a subsequent reduction in local tissue blood flow in response to central hypovolemia is a major cause for the observed reduction in regional tissue oxygenation.

As we have previously reported, the inability of the InSpectra probe to detect changes in  $S_{mO_2}$  during progressive reductions in central blood volume is disconcerting given that this device is currently used by the clinical community.<sup>15</sup> Although it has been suggested that the thenar is not the



**Figure 2.** InSpectra  $StO_2$  (open circles,  $n = 8$ ) and UMMS  $S_{mO_2}$  (closed circles,  $n = 8$ ) during progressive LBNP. Values are mean  $\pm$  SE. \* $p < 0.05$  compared with baseline. Figure modified from Soller et al.<sup>15</sup>



**Figure 3.** A, Linear relationship between  $S_{mO_2}$  and SV at each LBNP level. B, Inverse linear relationship with TPR. Values are mean  $\pm$  SE ( $n = 27$ ) for all parameters.

appropriate measurement site,<sup>16,17</sup> the InSpectra instructions for use directly state that it should be used on the thenar. It should be appreciated that the identification and removal of individual-specific spectral features is critical for an accurate NIRS-based assessment of tissue oxygenation. In this regard, the UMMS 2-source design uses algorithms that remove individual-specific spectral variation from skin and fat, whereas the InSpectra design does not include such a correction. In addition, the InSpectra sensor is not designed to collect light from deep within the muscle, having approximately half the source-detector spacing of the UMMS sensor. As such, the results of these experiments demonstrate that NIRS can be an effective technology for accurate noninvasive assessment of tissue oxygenation when sensors and algorithms are appropriately designed.

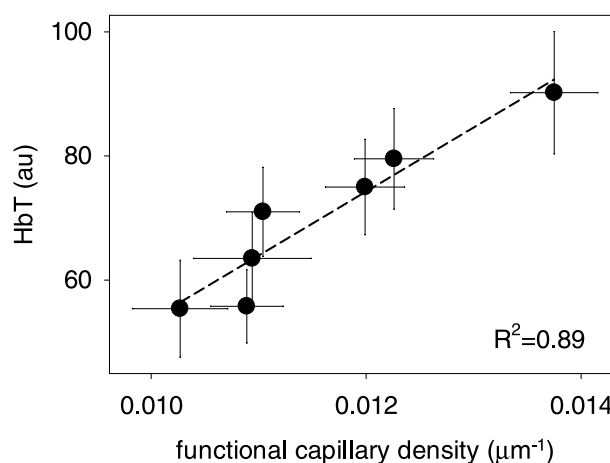
A previous bench study examined the relationship between HbT, the total absorber concentration, and the volume of absorber in the sensor field of view.<sup>7</sup> In the tissue, the absorber is hemoglobin, both oxygenated and deoxygenated forms. In the bench study, the NIR-absorbing dye was substituted for blood and the dye was contained in a set of capillary tubes. We examined the relationship between HbT and the number of tubes and showed that HbT tracked the volume of blood which was probed with the NIRS sensor, where a smaller number of tubes corresponded to a lower HbT.<sup>7</sup> We suggest that this model represents variation of the blood volume in the tissue, where a smaller number of tubes corresponds to vasoconstriction and a larger number of tubes, vasodilation. In the LBNP experiments, it was demonstrated that HbT measured in the forearm decreased linearly with FCD determined from the sublingual microcirculation (Fig. 4). These data suggest that, in the LBNP model as in hemorrhage, there is microvascular constriction in less critical tissues to compensate for the reduction in SV and preservation of systemic blood pressure and that HbT is an accurate measure of this vasoconstriction.

One of the earliest compensatory mechanisms in hemorrhage is sympathetically mediated reflex vasoconstriction.<sup>18</sup> During hemorrhage, vasoconstriction occurs predominantly in the skeletal muscle and splanchnic circulations to redirect blood flow to the heart and brain.<sup>19–21</sup> In this study, we have

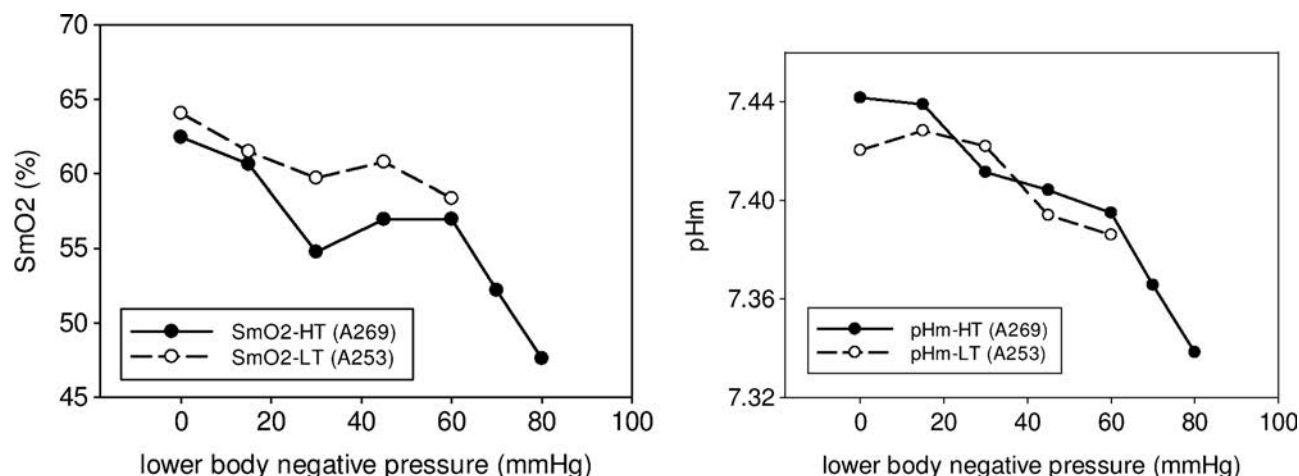
simultaneous assessment of both regions of circulation in a model of preshock hemorrhage; previous studies have indicated that the sublingual circulation can be considered a surrogate for blood flow reduction in the splanchnic circulation.<sup>22–24</sup> The high correlations between TPR and  $S_{mO_2}$  and between FCD and HbT provide compelling evidence that NIRS determination of HbT and  $S_{mO_2}$  can reflect early indication of blood loss and a warning that splanchnic organs may also be experiencing a reduction in oxygen delivery.

### Future Directions

Our use of LBNP as a model for the study of physiological mechanisms associated with cardiovascular collapse has revealed the existence of subject populations with either high (HT) or low (LT) tolerance to progressive reductions in central blood volume.<sup>25,26</sup> We have begun analyses for comparison of the  $S_{mO_2}$  and  $pH_m$  responses to LBNP between these groups of subjects. Preliminary results suggest that HT



**Figure 4.** Linear relationship between HbT and FCD determined from the sublingual microcirculation. Values are mean  $\pm$  SE for all subjects ( $n = 16$ ). Figure modified from Ward et al.<sup>13</sup>



**Figure 5.**  $S_{mO_2}$  (A) and  $pH_m$  (B) for individual subjects with HT (closed circles) and LT (open circles) to LBNP.

subjects demonstrated greater reductions in  $S_{mO_2}$  with lower pH at the time of cardiovascular collapse compared with LT subjects. An example of  $S_{mO_2}$  and  $pH_m$  responses in an individual HT and LT subject is illustrated in Figure 5. These findings may suggest that tolerance to hemorrhage is associated with a greater capacity to divert more blood flow to the central circulation. Because LT individuals decompensate with less volume reduction, NIRS technology could help better understand the physiology of those patients at greatest risk for earlier development of overt shock.

### Clinical Translation

The fiber optic system used in the LBNP evaluations was translated into a 58-g solid-state system by Reflectance Medical, Inc. Clinical evaluation of two Reflectance Medical, Inc, prototype sensors has been initiated at the Queen Sirikit National Institute of Child Health in Bangkok, Thailand, on patients with dengue fever and dengue hemorrhagic fever (DHF). Dengue hemorrhagic fever shares many clinical features with trauma-induced hemorrhage and shock, including

tachycardia, reduced pulse pressure, and hemoconcentration. Patients with DHF are most at risk for shock in the 48-hour period that surrounds the time of fever break (defervescence). We hypothesized that DHF patients who experienced intravascular volume depletion and subsequent hypovolemia would present with a significant reduction in  $S_{mO_2}$ , similar to that observed in the subjects with LBNP. Preliminary results support this hypothesis. The  $S_{mO_2}$  data obtained from one of the study patients are presented in Figure 6. Before defervescence (time 0),  $S_{mO_2}$  fluctuated between 40% and 60%. However, at 5 hours after defervescence,  $S_{mO_2}$  began a steep decline similar to that previously observed with the subjects with LBNP.

### Conclusions

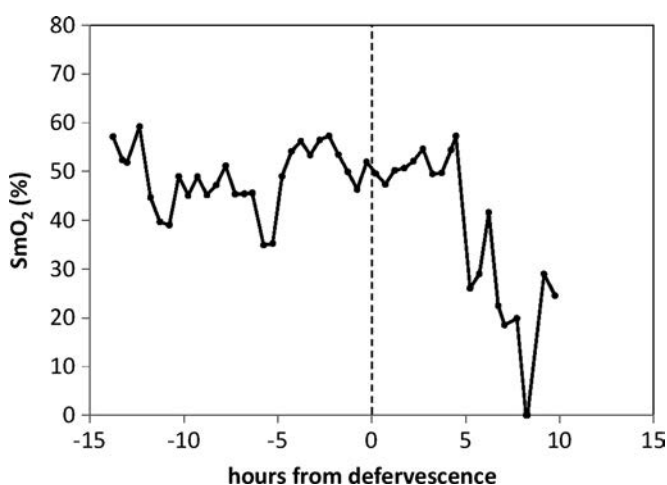
Using laboratory and clinical models of hemorrhage in humans, noninvasive determination of  $S_{mO_2}$  and  $pH_m$  has been shown to provide an early indication of compensated shock in comparison with standard vital signs. The results from these experiments provide evidence that NIRS technology offers a potentially powerful clinical tool for early diagnosis of patients with hemorrhage that is noninvasive, small, lightweight, and easy to use. Further studies on critically ill patients are planned to validate the usefulness of NIRS in the clinical setting for individualized diagnoses of blood volume status.

### AUTHORSHIP

All of the authors participated in data analysis and reviewed the article. V.A.C., K.L.R., and C.A.R. designed and conducted the LBNP experiments. K.W. was responsible for the portion of the study to measure FCD. B.R.S. was responsible for the NIRS work, including design of the sensor system and development of the pH algorithm. F.Z. developed the  $S_{mO_2}$ /HbT algorithms.

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**Figure 6.** The  $S_{mO_2}$  response of a single patient with DHF before and after defervescence (time 0).

## DISCLOSURE

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